

have needed to go forward and encourage the enrollment and recruitment of subjects from more vulnerable populations than we ever have: children, the elderly, ethnic groups.

We have had to face changes in the whole clinical trial system, the way it's conducted, the outsourcing of trials, new technologies, not only from the standpoint of how information is acquired and transmitted by electronic means, for example, but certainly also new technologies, as science has advanced to the point where basic science moved into clinical research, and we have certainly a more sophisticated level of applications that we're seeing now for review at both the research permit, the IND stage, and at the NDA stage. This is very much an area of global expansion.

Well, we certainly know over the past few years we've seen a large number of calls to action in the area of clinical research, a great deal of press attention. I can't say that the IG report back in June of '98 was by any means the first, nor had we not recognized some of the problems that the

IG reported back in '98, but it began to certainly consolidate thinking and bring a great deal of public attention to this area, to the concept that institutions were having difficulties in their oversight of clinical research. Resources weren't adequate at the institutional level. IRBs were overworked.

In reports in the New York Times, the concept that we still have cases of very, very marked clinical investigator fraud. We still have deaths in clinical trials. Some we would like to think perhaps are preventable, and indeed a death in a gene therapy trial in September of '99 certainly got a great deal of attention. Problems that we've seen abroad have gotten a great deal of attention in the press, the Washington Post series this past December, and even very recently, a death in what one would consider an academic research trial, certainly a trial that was not being forwarded for purposes of commercialization, but nonetheless a trial that used an investigational product, a drug by our definition, in a clinical

investigation.

We are certainly trying to answer these calls, and I'll talk a little bit about how we're going about doing this in just a moment. Ultimately, in answering these calls we really are very much based on our mission, and it is certainly a very broad public mission. We have to be out there ensuring the safe use of all of the products we regulate, 25 percent of the U.S. economy, or close to it, and make sure that those products themselves are safe and efficacious.

And to do this we need the information that comes from clinical research. We need the science that's underlying our decision-making, much of what has been talked about all day today. We need the accuracy, the completeness of information from good clinical trials.

Our mission is very broad, even from the standpoint of what we have to oversee in the clinical trial arena. We call it Good Clinical Practice, but it is very all-encompassing, very all-embracing. It's not simply domestic, it's very

much a global issue.

But fortunately we have colleagues in this process. GCP is, as it has been developed, very much a system of shared responsibilities, and that is the system that in fact we want to keep as vital as possible. We think it has done a very good job of protecting human research subjects over the past 25 years.

And in fact when we look at those few cases that I mentioned in the earlier slide where we've had deaths, we can actually look at this list of responsibilities and say in those cases we've lost some of the control points in each of those cases that would otherwise ensure the appropriate oversight of clinical trials, either by the investigator and the sponsor becoming one, the IRB simultaneously failing, the failure to bring these to the attention of government regulators to be able to interact in these clinical trials.

We have been very lucky, as well. Not only do we have the built-in colleagues that come from the shared system of responsibilities in GCP,

we also have a number of colleagues in government and a number of new government entities, if you will, or new people coming into government entities to revitalize this process. We're working very closely right now with the Office for Human Research Protections in the department to try to develop human subject protection as a unified entity, working as a single voice across government.

We're even extending that beyond the department, working with the National Science and Technology Committee's Subcommittee on Human Subject Research. This is a group of representatives from all the agencies that are involved in human research, behavioral, social, as well as biomedical. And we've seen a lot of new infrastructures coming into play, the VA putting in its own series of systems, again for research compliance, for research assurance, for furthering the oversight of clinical trials. New advisory committees coming down the line, as well as advisory committees to our own department, the

National Human Research Protection Advisory Committee.

But at the end of the day, though, we have all of these colleagues to work with, but we are still in some measure left on our own because FDA certainly has very unique responsibilities, responsibilities that ultimately play on decision-making in applications.

So what are we doing to address the issues that we've seen, the problems that have come to public attention, the problems that are threatening the ability in fact to even conduct clinical research because they're scaring off subjects from enrolling in clinical trials? We obviously have to address these concerns and make sure, in fact, that FDA is out at the forefront assuring that these protections are in place.

So we're looking at this from the standpoint of broad initiatives, initiatives to further protection of human research subjects, initiatives directed at defining and improving the responsibility of those who are involved in the

clinical research process, looking at reporting to FDA, trying to pull in and trying to enhance the reporting of problems to FDA so that in fact we can help work toward creative solutions in dealing with them. Ultimately, as well, issues in education and outreach.

And I'll talk also a little bit about how we're moving in these directions through an infrastructure that we put in place, the Office for Good Clinical Practices, and the collaborations out of there.

Well, first of all, protection. We know that there are a number of areas that we certainly have to strengthen and that we are working to strengthen. These aren't the level of the IRBs and institutions, looking at issues in real-time oversight of safety. It's not simply enough to come in after the fact, after the damage has been done. Looking at effective sponsor monitoring, not simply rote sponsor monitoring but mechanisms that will make the clinical trial process better. Strengthening our system with regard to clinical

investigators and site staff, as well as our own responsiveness to subject concerns and complaints.

Well, let's talk a little bit again about how we're moving to strengthen the IRB system. One very fundamental criticism that was brought our way by the Inspector General was that we don't even know the entire spectrum of IRBs that are out there, involved in FDA regulated research. So we have taken to heart the concept of moving toward IRB registration, not simply just to define an inventory but because now we have information technology capabilities available that, as we do put in place an IRB registration, it can be a two-way system that gives us the ability not only to know who is out there doing our work, but to be able to tell them what is new in that area, what we can come to expect in this area.

We're working with the Institute of Medicine and with OHRP, the Human Subject Research Subcommittee, toward at least piloting accreditation of IRBs. The goal is to raise the floor above our minimal regulatory requirements,

and we think the best way to do that is to move to an accreditation system that will largely be outside of government, where the standards in fact will help to promote improvements in the process.

And I think very much the third point is one we have to take into account, and that is to start reducing unnecessary burdens on IRBs and institutions where these are adding little to human subject protection, or indeed where they are already covered, covered by industry, covered by us, or otherwise better covered by systems that we perhaps have to still think about but put in play.

So, again, the challenges for us are still, one, we have a whole series of human subject protection functions that we need to cover. We know that this includes a review of the ethics, a review of consent, scientific review, general monitoring of studies, specific safety monitoring of studies and real-time safety monitoring. We have to make sure conflict of interest isn't at issue, and we still have concerns about maintaining privacy and confidentiality.

continual quality improvement, that we are making strides in this whole process.

We are working as well in the area of real-time oversight of safety. Part of this we know. The only group that can effectively, or the only individual that can effectively ensure the safety of a subject, outside of the subject his or herself, is going to be the person with direct contact, and that's the clinical investigator or site staff. I think we're all fooling ourselves if we think that parties very remote to the subject and the investigator are going to accomplish this.

So we have to spend time on education and on changing institutional culture to ensure, if we have cases where an investigator is also the sponsor of a study, they understand that that doesn't mean they have to do less because no one is monitoring them. Rather, it means they have twice the responsibility and twice the need for education in what they need to do properly.

We're moving from the standpoint of oversight of safety in looking at other structures,

though. I mentioned this earlier, and one of these is certainly the Data Monitoring Committee. And I am actually very pleased to say FDA's guidance, our draft guidance on data monitoring, issued on our web sites this morning. It is a fortuitous time because in fact we had long ago planned to have a public workshop on data monitoring committees scheduled for the 27th of November here in Bethesda, and we are pleased to see that the guidance document is available, such that it can be discussed in time for that meeting.

And we're working as well with NIH, with OHRP, in discussion of safety databases. We're also working in the area of protecting vulnerable populations. As I said, part of the goal is for FDA to speak with one voice across government, and one of the ways we have done this is by starting to look at those regulations, those areas that we can promote protection, that are otherwise part of government regulation, such as the PHS regulations for children, and have moved to adopt these. And so Subpart B of the interim rule, which looks at

safeguards at the level of the IRB, is now part of FDA regulation as an interim rule we put into place in April of this year.

We are starting to look down the line in other ways to look at consistency, looking at Subpart B, for example, another PHS subpart dealing with protections for pregnant women and neonates. We are looking also to enhance our bio research monitoring program. It's always difficult. Our Office for Regulatory Affairs, our field force, has always had to suffer from continual declines in resources, from continual pulling away of resources from the bio research monitoring arena, but I think now we can say we may have some success in moving toward more resources in this area.

But again, like with our other strategies, we have to use these resources very wisely. We have to use them in a strategic planned fashion, and part of this means we need to take on a balance between how we look at clinical trials. We need of course to keep looking at trials as they are submitted for purposes of FDA decision-making, to

ensure the integrity of the information that we get, but we also need to use those resources to be responsive to the public, to the community, by following up on real-time complaints, and also to promote the science of what we are doing in our bio research monitoring program.

It's important to know at some level the state of affairs in areas that are coming to the forefront scientifically or that are involving vulnerable populations. We started this with gene therapy, doing a more systematic statistical look. Certainly we're going to move down this row in other areas. I put pediatric trials up here because that's one area I certainly would like to see focused upon. I'm not sure we have yet made our decisions entirely where we are going to next prioritize.

But in any case, as we are moving forward, we are moving forward with other groups as well. We have started information sharing with OHRP, with the VA, with others, to make sure in fact that we are not simply preventing compliance information

that's important to all of us from going forward.

And you've heard a lot about quality. Quality assurance is going to be part of our system. We know we need to look not only externally and promote to industry that they should have quality assurance programs and quality improvement programs. That's kind of a hollow advice to industry, if we ourselves are not doing the same with FDA, such that we can assure industry and the community are getting consistent advice from us.

Well, I said before, part of this also is responsibility. We have to be out there ensuring understanding. Right now, of course, based on issues I had mentioned with recent deaths in an academic setting, we have to reiterate what in fact our law, what our regulations currently state. Our law defines "drug" very broadly, and in fact it is, as indicated here, one of the definitions is "articles (other than food) to affect the structure or any function of the body of man."

So you can see, I mean, our coverage, what

we are responsible for in regulating these products under the law is very broad, and similarly clinical investigation in our regulations is defined very broadly. It's essentially, for an approved product, any use in medical practice, any experiment that involves a drug or a test article. And indeed, under our regulations, when an unapproved drug or product is used in a clinical investigation, there is a requirement for FDA to be part of the regulatory scheme. That's how it currently exists.

So the challenge for us, of course, is now we have to reiterate that message, that challenge studies, physiology studies of unapproved drugs, biologics, and significant risk devices certainly meet the definitions for FDA jurisdiction. But we also need to be cognizant of how that's going to impact science and how that's going to impact the community, by understanding the nature and scope of these activities in the community, and ultimately coming to work with the community to define how we can balance our level of oversight with the level

of risk in these studies.

We also know that for a long period of time we have had a lot of ambiguity in what the FDA definitions read, such that this has created loopholes and confusion in the clinical trial arena. I don't think any of us in FDA ever thought of the concept of a subinvestigator or, excuse me, an investigator being 3,000 miles removed from any physical or verbal contact with a patient, but simply an administrator in an office, while everyone else is a subinvestigator. That's certainly not what ICH, the International Conference on Harmonization, has put forward, and I don't think that that's what any of our thinking would be, but that's not clear from our definitions.

We have those intrinsic problems, as I said, with sponsor/investigators. If GCP is a system of controls, what happens when the sponsor and the investigator are the same? They are silly questions in some ways. I mean, the sponsor is responsible to provide the investigator with an

investigator brochure. What does this mean, that the person gives it to themselves? The sponsor is responsible for monitoring the investigator. What does that mean in a sponsor/investigator study? The person is supposed to monitor themselves without any additional oversight?

These are real problems for us right now. And similarly there are the problems of what are the responsibilities of institutions? We said IRBs can't do it all. FDA certainly regulates institutions. We have to talk a little bit with the community about what institutions can and should do.

It's certainly an issue as well of conflict of interest. We are working as part of a broader group with OHRP, with the National Human Research Protection Advisory Committee, the Human Research Subject Subcommittee, to develop guidance that will help promote minimization and managing of conflicts of interest, not simply payments but any kind of potential conflict of interest, and not simply for the investigator but also at the

institutional level.

We also have to look again at non-U.S. trials. The Inspector General has just told us that we've seen a 16-fold increase in the number of non-U.S. clinical investigators submitting data to FDA applications over the past 9 to 10 years. That's certainly a very large increase, but one that you would expect with the globalization of the industry.

We have to look back at our criteria for accepting these studies. We didn't have standards, we didn't have GCP defined when we put most of these regulations in place, and we rooted our acceptance in very vague ethical principles such as those in the early versions of the Declaration of Helsinki. We've moved a long ways in that area on an international level. Certainly much of the world, even China, is now adopting GCP standards, ICH GCP standards. I think it's time we update our own expectation. You know, we expect more than just vague ethical conformance. We want good science, we want good quality, and we also want

good human subject protection.

And we've made a great deal of progress in GCP harmonization. We're looking toward GCP as a more concrete standard, and as we do that, we're looking also toward venues in which we can further globalize these standards. The World Health Organization is interested in this. They have recently convened a consultation that we were part of. Pan American Health Organization as well, in the device area they're moving forward through ISO. And as well we're looking at mechanisms for supporting capacity building.

We also need to deal with issues of misconduct. We've talked with various of the trade organizations about this, because in fact we worry that there are loopholes in the current regulatory schema. The concept that in fact only the clinical investigator is subject to termination with regard to falsification, this is a matter that takes place only if the sponsor can't correct. And if the trial is over, what does that mean? You obviously can't correct when the trial is over, but yet that

is a loophole in terms of reporting.

So we're looking back at what we expect to keep scientific validity in an appropriate position, and we're looking at this even from the standpoint of regulation.

Well, there is no question education is ultimately going to be the key. We need to target all who participate. We're looking at technology. We've moved into web sites that are going to provide access to GCP information in consolidated spots.

This is our new office's web site, and I'll say a little bit more about that very briefly. One of the things that certainly we have decided to do within the agency, and I certainly thank our leadership council for that decision, is to establish an umbrella office, a new office to coordinate GCP across the agency as well as beyond the agency.

We had a few abortive attempts at naming this office. Those of you who have followed this perhaps in the trade press, we started off as an

Office of Clinical Science. I think we all agreed that this embraces perhaps more than clinical science, embraces all aspects of Good Clinical Practice. We tried Office for Human Research Trials, with the hope that this would give the impression of our coordinated work with Office for Human Research Protection at the department. Unfortunately it created a great deal of confusion instead, so we settled on the Office for Good Clinical Practice. It is a very small office. We're going to remain it as a very small office, but it is strategically located within the Commissioner's Office and our Office of Science.

The key positions are the directorship and two other positions that we certainly moved forward with. Stan Woollen's position is Associate Director for Bio Research Monitoring. Stan has had some 25 years of experience or 23 years of experience in the bio research monitoring arena, at all levels from field to ORA management to Center level and now to our umbrella office. And Bonnie Lee, who has been involved with FDA in the area of

ethics issues from the time of the National Commission and the Tuskegee studies, again a very long-experienced person in the area of human subject protection policy.

So our role here, we're taking on a centralized role as a small office, to largely try to bridge the Centers and ORA in the development of GCP policy, in developing those quality systems for our own bio research monitoring program and promoting quality in clinical trials externally, in many of the initiatives I've indicated earlier, in our agency international harmonization efforts in the GCP arena, and coordinating GCP education and outreach.

In remaining small, we have to rely on leveraging, and so this affects--again, I am very thankful for the cooperation of our senior management, our leadership council, by providing our group with the resources of the key medical policy-makers and key compliance policy-makers within the agency to come together in steering committees, roundtables, and working groups to deal

with these problems. So we don't have to manage them from a top-down perspective, but we can actually pull in operational knowledge from the strongest people in all of the Centers. We're leveraging with OHRP and ultimately leveraging with our stakeholders.

So in conclusion I would like to say we are moving forward, but there are certainly a lot of opportunities where we need to work together as an agency and we need to work together with all of our constituency groups. The reforms are underway here, but the only way we are going to make these systems improve and get the best possible systems is to get our broadest possible participation.

So I thank you very much for your time and attention, and I will be taking questions.

CHAIRMAN LANGER: Questions or comments from anyone? Okay, thank you very much.

Comments in general from the Science Board?

Another comment? Yes.

MS. MOENCH: Yes, I would like to ask a

question if you don't mind. Liz Moench from MediciGroup, and I really want to thank Dr. Lepay for an excellent presentation. I think there are a couple of things, as I listened to this presentation, that I'd like to ask for consideration on.

Number one is, I think that we have to give very careful consideration to the role of the PI. The PI is, I think needs to be redefined, not as a physician investigator but actually as practically invisible or partially involved. In a study that we just completed, I can tell you that out of 100 PIs, only two were actually actively seeing patients. So what we're seeing is a very concerning trend where it is the study coordinator who is playing a much more involved role in clinical research today, and not the PI.

So I think that that is an issue that is certainly going to rear its head in clinical litigation, because we're certainly seeing more and more law firms getting into this, and maybe then sponsors will play a more active role in setting

performance standards. But I think that maybe FDA, in collaboration with the AMA, could play a role in more certification. I like the idea of IRB certification, but I would certainly like to see greater certification of physician investigators who actually really realize what their role should be and what the consequences are.

I think the other point I would like to raise also is that we really need to look at overhauling the informed consent process. I can tell you when we do comprehension testing, many patients have no idea really what they're signing. And there is some marvelous literature now out there that actually shows how few patients really comprehend in fact that they are even participating in a clinical trial. So I would really like to see that and some more comprehension testing, that sponsors in fact have to demonstrate that the patients really do understand. I know Lou Morris did so much work looking at comprehension testing of labeling of OTC products. Really this is comparable, I think, to that process.

And finally, I would really like to see that we get more in terms of quality check, in terms of patient feedback. I know that we have played a role with some sponsors in actually doing satisfaction testing, where we actually get feedback directly from patients and their experience in clinical trials, and I can tell you it has been an eye opener to some of the clinical teams.

So those are some points that I would like to raise, and I thank you very much.

DR. LEPAY: Just briefly.

CHAIRMAN LANGER: Very briefly.

DR. LEPAY: I was just going to say those are three certainly very good points, and from the perspective of clinical investigators, this is something that we have targeted as an issue for the past two or three years. We're working with the AAMC. We've worked with a number of medical schools and medical colleges that have come forth and within their own institutions have put into place, or tried to put into place, certification

programs or certification requirements. We thought that that was a good use of FDA resources in contributing to educational programs.

On the realm of IRBs and informed consent, I think you're absolutely right, and I think the only way we are going to achieve a better informed consent process is to pull IRBs back to basics, to say in fact the informed consent is one of the leading roles of the IRB, and we would much rather focus some level of time and attention on quality assuring and quality improving the process of informed consent, and maybe less on some of the less important, less protective issues that they have come to acquire over the years, and we have to move forward in restructuring that aspect of the system.

DR. LEPAY: Thank you. So just briefly, a summary, I think what we concluded today is that the pharmaceutical manufacturing issues that were raised this morning were very important. I want to encourage the FDA to move forward on that and to keep us informed. And we certainly accept the

CDRH's External Science Review. It's very positive. So thank you all very much, and we'll look forward to the next meeting.

[Whereupon, at 4:00 p.m., the meeting was adjourned.]